

CLAIMSREPLACED BY
ART 34 AMDT

1. Use of a penetrant, suspended or dispersed in a solvent, in the form of a minute fluid droplet surrounded by a membrane-like coating of one or several layers of at least two different substances or two different forms of a substance with the tendency to aggregate, said substances or forms of a substance differing by at least the factor of 10 in the solubility in a preferably aqueous, liquid medium, such that the average diameter of homo-aggregates of the more soluble substance or form of the substance or the average diameter of the hetero-aggregates consisting of both said substances or forms of said substance is smaller than the average diameter of homo-aggregates of the less soluble substance or form of the substance and/or wherein the more soluble component tends to solubilise the penetrating droplet and wherein the content of such component amounts to up to 99 mol-% of the concentration required to solubilise the droplet or else corresponds to up to 99 mol-% of the saturating concentration in the un-solubilised droplet, whichever is higher, and/or wherein the elastic deformation energy of the droplet surrounding the membrane-like coating is at least 5x lower, more preferably is at least 10x lower and ideally is more than 10x lower than that of the red blood cells or of the phospholipid bilayers with fluid aliphatic chains, such droplets then acting as carriers for the transnasal administration of a pharmaceutically active compound, an antigen, an allergen, a mixture of antigens and/or a mixture of allergens.

2. Use of a penetrant, suspended or dispersed in a solvent, in the form of a minute fluid droplet surrounded by a membrane-like coating of one or several layers of at least two different substances or two different forms of a substance with the tendency to aggregate, said substances or forms of a substance differing by at least the factor of 10 in the solubility in a preferably aqueous, liquid medium, such that the average diameter of homo-aggregates of the more soluble substance or form of the substance or the average diameter of the hetero-aggregates consisting of both said substances or forms of said substance is smaller than the average diameter of homo-aggregates of the less soluble substance or forms of the substance and/or wherein the more soluble component tends to solubilise the penetrating droplet and wherein the content of such component amounts to up to 99 mol-% of the concentration required to

solubilise the droplet or else corresponds to up to 99 mol-% of the saturating concentration in the un-solubilised droplet, whichever is higher, and/or wherein the elastic deformation energy of the droplet surrounding the membrane-like coating is at least 5x lower, more preferably is at least 10x lower and ideally is more than 10x lower than that of the red blood cells or of the phospholipid bilayers with fluid aliphatic chains as a carrier for the preparation of a pharmaceutical, preferably a vaccine composition for transnasal administration.

3. Use of a penetrant, suspended or dispersed in a solvent, in the form of a minute fluid droplet surrounded by a membrane-like coating of one or several layers of at least two different substances or two different forms of a substance with the tendency to aggregate, said substances or forms of a substance differing by at least the factor of 10 in the solubility in a preferably aqueous, liquid medium, such that the average diameter of homo-aggregates of the more soluble substance or form of the substance or the average diameter of the hetero-aggregates consisting of both said substances or forms of said substance is smaller than the average diameter of homo-aggregates of the less soluble substance or form of the substance and/or wherein the more soluble component tends to solubilise the penetrating droplet and wherein the content of such component amounts to up to 99 mol-% of the concentration required to solubilise the droplet or else corresponds to up to 99 mol-% of the saturating concentration in the un-solubilised droplet, whichever is higher, and/or wherein the elastic deformation energy of the droplet surrounding the membrane-like coating is at least 5x lower, more preferably is at least 10x lower and ideally is more than 10x lower than that of the red blood cells or of the phospholipid bilayers with fluid aliphatic chains, said penetrant being used in combination with a pharmaceutically active ingredient or an allergen or an antigen for the preparation of a transnasally administerable pharmaceutical composition for the treatment of infective diseases, endocrine disorders, preferably hypopituitarism, diabetes, hyperthyroidism, thyroiditis, most preferably Hashimoto's thyroiditis, subacute thyroiditis; adrenal disorders, preferably Addison's disease, secondary adrenal insufficiency, Cushing's syndrome; gastrointestinal disorders, preferably Crohn's disease, colitis; hemorrhagic diseases, preferably hemophilia, leukopenia, hypereosinophilic syndrome; musculoskeletal and connective tissue disorders, preferably rheumatoid arthritis, Sjögren's syndrome, Bechet's

syndrome, lupus, scleroderma, polymyositis/dermatomyositis, polymyalgia rheumatica and temporal arthritis, polyarteriosis nodosa, Wegener's granulomatosis, mixed connective tissue disorder, ankylosing spondylitis, psoriatic arthritis, osteoarthritis, Paget's disease, sciatica, bursitis, tendonitis and tenosynovitis, epicondylitis, fibromyalgia, eosinophilic faciiitis; neurological disorders, preferably pain, singultus, vertigo, seizure disorders, sleep disorders, transient ischemic attacks, spinal cord injury, demyelinating diseases, nerve root disorders, myasthenia gravis; oncological disorders; psychiatric disorders, preferably drug dependence, neuroses, mood disorders, schizophrenic disorders, delusional disorders; and/or for use in the field of gynecology, preferably for the treatment of dysmenorrhea, menopause, chronic anovulation, premature ovarian failure, endometriosis, infertility; and/or for use in the field of immunology, preferably transplant rejection, hyposensitisation, allergen immunotherapy or prophylactic vaccination.

4. A pharmaceutical composition for transnasal administration comprising a carrier, which is a penetrant, suspended or dispersed in an aqueous solvent, in the form of a minute fluid droplet surrounded by a membrane-like coating of one or several layers of at least two different substances or two different forms of a substance with the tendency to aggregate, said substances or forms of a substance differing by at least the factor of 10 in solubility in a preferably aqueous, liquid medium, such that the average diameter of homo-aggregates of the more soluble substance or form of the substance or the average diameter of the hetero-aggregates consisting of both said substances or forms of said substance is smaller than the average diameter of homo-aggregates of the less soluble substance or form of the substance and/or wherein the more soluble component tends to solubilise the penetrating droplet and wherein the content of such component amounts to up to 99 mol-% of the concentration required to solubilise the droplet or else corresponds to up to 99 mol-% of the saturating concentration in the un-solubilised droplet, whichever is higher, and/or wherein the elastic deformation energy of the droplet surrounding the membrane-like coating is at least 5x lower, more preferably is at least 10x lower and ideally is more than 10x lower than that of the red blood cells or of the phospholipid bilayers with fluid aliphatic chains said composition also including a

pharmaceutically active ingredient, an allergen, an antigen, a mixture of antigens and/or a mixture of allergens.

5. The use of claim 3 or the pharmaceutical composition of claim 4 wherein the pharmaceutically active ingredient is an adrenocorticostaticum, an adrenolyticum, an androgen or antiandrogen, an antiparasiticum, an anabolicum, an anaestheticum or analgesicum, an analepticum, an antiallergicum, antiarrhythmicum, antiarteroscleroticum, antiasthmaticum and/or bronchospasmolyticum, an antibioticum, an anti-infective agent, antidepressivum and/or antipsychoticum, an antidiabeticum, an antidot, an antiemeticum, antiepilepticum, antifibrinolyticum, anticonvulsivum or anticholinergicum, an enzyme, a coenzyme or the corresponding enzyme inhibitor, an antihistaminicum (and combinations thereof) or antihypertonicum, an antihypotonicum, anticoagulant, antimycoticum, antimyasthenicum, an agent against Morbus Alzheimer or Morbus Parkinson, an agent for ACS therapy, an antiphlogisticum, antipyreticum, antirheumaticum, antisepticum, a respiratory analepticum or a respiratory stimulant, a broncholyticum, cardiotonicum, chemotherapeuticum, a coronary dilatator, a cytostaticum, a diureticum, a ganglium-blocker, a glucocorticoid, an anti-flew agent, a haemostaticum, hypnoticum, an immunoglobuline or its fragment or any other immunologically active substance, such as an immunomodulator, a bioactive carbohydrate (derivative), a contraceptive, an anti-migraine agent, a corticosteroid, a muscle relaxant, a narcoticum, a neurotherapeuticum, a (poly)nucleotide, a neurolepticum, a neurotransmitter, a (poly)peptide (derivative), an opiate, an ophthalmicum, (para)-sympaticomimeticum or (para)sympathicolyticum, a protein(derivative), a psoriasis/neurodermitis drug, a mydriaticum, a psychostimulant, rhinologicum, a sleep-inducing agent, a sedating agent, a spasmolyticum, tuberculostaticum, urologicum, a vasoconstrictor or vasodilatator, a virustaticum, a wound-healing substance, an alcohol abuse preparation, an anticonvulsant, an antineoplastic, an antirheumatic, an appetite suppressant, a biological response modifier, a blood modifier, a bone metabolism regulator, a cardioprotective agent, a cardiovascular agent, a central nervous system stimulant, an enzyme, an agent for erectile dysfunction therapy, a fertility agent, a gastrointestinal agent, a gout preparation, a hormone, an agent for hypercalcemia management, an agent for hypocalcemia management,

an immunosuppressive, a migraine preparation, a motion sickness product, an agent for multiple sclerosis management, a muscle relaxant, a nutritional, an ophthalmic preparation, an osteoporosis preparation, an otic preparation, a parasympatholytic, a parasympathomimetic, a prostaglandin, a psychotherapeutic agent, a respiratory agent, a sedative & hyponotic, a skin & mucous membrane agent, a smoking cessation aid, a sympatholytic, a tremor preparation; a urinary tract agent, a vaginal preparation, a vertigo agent, an immunologically active substance (such as an immunomodulator, e.g., bacterial extracts or cell wall components like cholera toxin, heat labile toxin, monophosphoryllipid A, or cytokine inducing agents or hormones like thymosin, thymulin, thymopietin, or phytoimmunostimulants like extracts from Echinacea root, wild indigo root, white cedar leave tips, or synthetic immunomodulators like quinoline derivatives, synthetic peptides, pyrimidine, lipopeptides, or cytokines or immunosuppressants, and signal transduction inhibitors like cyclosporin A, FK506, FTY720, rapamycin), an inhibitor (antagonist), or a promotor (agonist) of the activity of any of above mentioned agents, or any combination of said active substances.

6. The use of claim 3 or the pharmaceutical composition of claim 4 wherein the antigen is derived from a pathogen.

7. The use of claim 3 or the pharmaceutical composition of claim 4 wherein said pathogen belongs to extracellular bacteria, including pus-forming cocci, such as *Staphylococcus* and *Streptococcus*, gram-negative bacteria, such as Meningococcus and Gonococcus species, species of *Neisseria*, gram negative bacteria, including enteric organisms such as *E. coli*, *Salmonella*, *Shigella*, *Pseudomonas*, *Diphtheria*, *Bordetella Pertussis*, and gram-positive bacteria (e.g. *Bacillus pestis*, BCG), particularly anaerobes, such as the *Clostridium* species (e.g. *Clostridium tetani*, *Clostridium perfringens*, *Clostridium novyi*, *Clostridium septicum*), bacteria and viruses, which survive and replicate within host cells, comprising mycobacteria (e.g. *M. tuberculosis*) and *Listeria monocytogenes*, retro- and adenoviruses, including hepatitis virus, (human) immunodeficiency virus, herpes viruses, small-pox (chicken-pox), influenza, measles, mumps and polio viruses, cytomegalovirus, rhinovirus, etc., and fungi prospering inside host cells, a parasite including animal parasites, such as protozoa and helminths,

and ectoparasites, such as ticks and mites, or *Brucella* species, (e.g. *B. melitensis*, *B. abortus*, *B. suis*, *B. canis*, *B. neotomae*, *B. ovis*, the causative agent for cholera (e.g. *Vibrio cholerae*), *Haemophilus* species like *H. actinomycentemcomitans*, *H. pleuropneumoniae*, as well as pathogens triggering paratyphoid, plague, rabies, tetanus and rubella diseases or to eukaryotic cells or their parts that cause various neoplasiae, auto-immune diseases and other pathological states of the animal or human body which do not necessarily result from microbial infections.

8. The use of claim 3 or the pharmaceutical composition of claim 4 wherein the antigen is used in a purified or even better in a pure form.
9. The use of claim 3 or the pharmaceutical composition of claim 4 wherein the antigen is the antigenic determinant of hepatitis virus, (human) immunodeficiency virus, herpes viruses, small-pox (chicken-pox), influenza, measles, mumps and polio viruses, cytomegalovirus, rhinovirus, etc., and fungi prospering inside host cells, a parasite including animal parasites, such as protozoa and helminths, and ectoparasites, such as ticks and mites, or *Brucella* species, including the causative agent for cholera, *Haemophilus* species, as well as pathogens triggering paratyphoid, plague, rabies, tetanus and rubella diseases or else eukaryotic cells or their parts that cause various neoplasiae, auto-immune diseases and other pathological states of the animal or human body, which do not necessarily result from microbial infections.
10. The use of claim 3 or the pharmaceutical composition of claim 4, wherein the allergen is of xenogenic or endogenic origin, derived from a microorganism, an animal or a plant, or belonging to the group of man made and/or irritating inorganic substances, or to such parts or components of the human body which were incorrectly processed by or exposed to the body immune system.
11. The use of claim 3 or the pharmaceutical composition of claim 4 wherein the allergen belongs to the class of the inhalation allergens, including but not limited to various pollen, spores, bits of animal hair, skin, feather, natural and synthetic textiles, wheat, (house) dust, including mite; furthermore, food and drug allergens; contact allergens; injection, invasion or depot allergens, such as

various (gastrointestine-resident) worms, echinococci, trichines, etc., a part of implantation material.

12. The use of any one of claims 1 to 3 and 5 to 11 or the pharmaceutical composition of any one of claims 4 to 9 additionally comprising a compound which releases or induces cytokine or anti-cytokine activity or exerts such an activity itself.
13. The use or the pharmaceutical composition of claim 12 wherein the compound exerting cytokine activity is IL-4, IL-3, IL-2, TGF, IL-6, TNF, IL-1 α and/or IL-1 β , a type I interferon, preferably IFN-alpha or IFN- β , IL-12, IFN- γ , TNF- β , IL-5 or IL-10.
14. The use or the pharmaceutical composition of claim 12 wherein said compound with anti-cytokine activity is an anti-cytokine antibody or the corresponding active fragment, a derivative, or an analogue thereof.
15. The use or the pharmaceutical composition of claim 4 wherein the compound displaying or inducing cytokine or anti-cytokine activity and the pharmaceutically active ingredient or antigen or allergen are associated with the penetrant.
16. The use of any one of claims 1 to 15 or the pharmaceutical composition of any one of claims 4 to 15 wherein the less soluble self-aggregating molecule is a lipid, preferably a polar lipid, and the more soluble component is a surfactant or some more soluble form of the polar/basic lipid.
17. The use of any one of claims 1 to 16 or the pharmaceutical composition of any one of claims 4 to 16 wherein the more soluble component is an agent to be transported across the barrier, said agent having a tendency to form common large structures with the less soluble component(s) of the penetrant, typically in the form of a physical or a chemical complex.
18. The use of any one of claims 1 to 17 or the pharmaceutical composition of any one of claims 4 to 17 wherein the more soluble component tends to solubilise the penetrating droplet and is present in concentration not exceeding 99 mol%

of the concentration required to disintegrate the droplet or, alternatively, not exceeding 99 mol% of the saturating concentration in the unsolubilised droplet, whichever is higher, values below 50% of the former relative concentration being particularly useful, with values below 40 rel-% or even around and below 30 rel-% being even more advantageous, whereas in the case of droplets which cannot be solubilised by the more soluble component relative concentrations which exceed the above mentioned relative concentrations by the factor of up to 2 are most preferred.

19. The use of any one of claims 1 to 18 or the pharmaceutical composition of any one of claims 4 to 18 wherein the less soluble penetrant component is a polar lipid and the more soluble component is a surfactant or a surfactant-like molecule or else such form of a lipid, preferably a polar lipid which is sufficiently soluble for the purpose of this invention.
20. The use of any one of claims 1 to 19 or the pharmaceutical composition of any one of claims 4 to 19 wherein the average penetrant diameter is between 25 nm and 500 nm, preferably between 30 nm and 250 nm, even more preferably between 35 nm and 200 nm and particularly preferably between 40 nm and 150 nm.
21. The use of any one of claims 1 to 20 or the pharmaceutical composition of any one of claims 4 to 20 wherein the penetrant concentration in the formulation for the use in human or animal nose is 0.001 to 20 weight-% of total dry mass in the formulation, in particular between 0.01 w-% and 15 w-%, more preferably between 0.1 w-% and 12.5 w-% and most preferred between 0.5 w-% and 10 w-%.
22. The use of any one of claims 1 to 21 or the pharmaceutical composition of any one of claims 4 to 21 wherein the supporting medium, e.g. a buffer, is selected to be a biocompatible solution with an osmotic activity similar to that of a monovalent electrolyte with concentration in the range between 1 mM and 500 mM, more preferably between 10 mM and 400 mM, even more preferably between 50 mM and 300 mM, and most preferably between 100 mM and 200

mM or else such solution that affords practically sufficient penetrant stability combined with practically sufficient transport rate across the barrier.

23. The use of any one of claims 1 to 22 or the pharmaceutical composition of any one of claims 4 to 22 wherein the relative drug or agent concentration is between 0.001 and 40 weight-% of total penetrant mass, in particular between 0.01 w-% and 30 w-%, even better between 0.1 w-% and 25 w-% and most preferably between 0.5 w-% and 15 w-%.
24. The use of any one of claims 1 to 23 or the pharmaceutical composition of any one of claims 4 to 23 wherein the medium supporting the drugs and carriers is a biocompatible buffer with pH value between 4 and 10, more frequently between 5 and 9 and most often between 6 and 8.
25. The use of any one of claims 1 to 24 or the pharmaceutical composition of any one of claims 4 to 24 wherein the additives are included in the preparation to reduce the system sensitivity to chemical, biological or ambient stress, including anti-oxidants, antagonists of undesired enzyme action, cryo-preservants, microbicides, etc., or else modulators of physically important system properties, such as formulation viscosity, etc..
26. The use of any one of claims 1 to 25 or the pharmaceutical composition of any one of claims 4 to 25 wherein the relative drug or agent dose to be administered non-invasively through the nose by means of highly adaptable carriers is chosen to be between 0.1x and 500x, more often between 0.5x and 250x, and even more preferably between 1x and 100x different from the corresponding drug or agent dose that would have to be injected to achieve the desired biological effects.
27. The use of any one of claims 1 to 26 or the pharmaceutical composition of any one of claims 4 to 26 wherein the applied penetrant dose is between 0.01 mg and 15 mg per nostril, even more often is in the range 0.1 mg and 10 mg per nostril, and preferably is between 0.5 mg and 5 mg per nostril.

28. The use of any one of claims 1 to 27 or the pharmaceutical composition of any one of claims 4 to 27 wherein the efficiency of administration and the biological effects of the agent or drug chosen are controlled by using different application volumes.
29. The use of any one of claims 1 to 28 or the pharmaceutical composition of any one of claims 4 to 28 wherein said formulation is administered using a metered delivery device.
30. The use of any one of claims 1 to 29 or the pharmaceutical composition of any one of claims 4 to 29 wherein different application volumes are selected to control the efficiency of administration and the biological effects of the chosen agent or drug.
31. The use of any one of claims 1 to 30 or the pharmaceutical composition of any one of claims 4 to 30 wherein the penetrants in suspension are loaded with the drugs or agents within 24 hours prior to the formulation administration, preferably 360 min, more preferably 60 min and even more preferably 30 min before the resulting formulation administration in the nose.
32. The use of any one of claims 1 to 31 or the pharmaceutical composition of any one of claims 4 to 31 wherein the delivery device is loaded at the treatment site.
33. The use of any one of claims 1 to 32 or the pharmaceutical composition of any one of claims 4 to 32 wherein the device is loaded separately with penetrants and the molecules, particularly biological agents, to be associated therewith.
34. The use of any one of claims 1 to 33 or the pharmaceutical composition of any one of claims 1 to 33 wherein the pharmaceutically active ingredient is for administration to the nervous system.
35. The use or the pharmaceutical composition of claim 34 wherein the nervous system is the brain.

36. The use of any one of claims 1 to 35 or the pharmaceutical composition according to any one of claims 4 to 35 wherein said pharmaceutical composition is a vaccine.
37. The vaccine of claim 36 which further comprises a pathogen extract or a compound from a pathogen or a fragment or a derivative thereof.
38. The vaccine of claim 37 wherein said pathogen extract or compound is selected from hepatitis virus, (human) immunodeficiency virus, herpes viruses, small-pox (chicken-pox), influenza, measles, mumps or polio viruses, cytomegalovirus, rhinovirus, etc., or fungi prospering inside host cells, a parasite including animal parasites, such as protozoa and helminths, and ectoparasites, such as ticks and mites, or *Brucella* species, including the causative agent for cholera, *Haemophilus* species, as well as pathogens triggering paratyphoid, plague, rabies, tetanus or rubella diseases.
39. The vaccine of any one of claims 36 to 38 which further comprises an adjuvant.
40. The vaccine of claim 38 or 39 wherein said adjuvant is lipopolysaccharide, such as lipid A or a derivative or modification thereof, such as monophosphoryl lipid A, or its analogue, such as a fatty derivative of saccharose, cord-factor (trehalose-dimycolate), muramyl dipeptide, or another (poly)saccharide or (poly)peptide identical to or resembling an immunologically active part of a membrane of a microorganism; an extract of a microorganism, including bacterial exo- and endotoxins, preferably cholera toxin or the heat labile toxin of *E. coli*, an A-chain derivative, a component with an ADP-ribosylating activity, a peptidoglycane, a clostridial toxin, an LT halotoxin, purified protein derivative of *M. tuberculosis*, LT-R192G, Fibronectin-binding protein I of *Streptococcus pyogenes*, or outer membrane protein of group B *Neisseria meningitidis* (GBOMP), bacterial or viral nucleic acids, such as oligonucleotides comprising unmethylated CpG dinucleotides.
41. The vaccine of any one of claims 36 to 40 comprising a blend of MPL and IL-12 or GM-CSF and IL-4.

42. The vaccine of any one of claims 36 to 41 wherein the relative immunogen/antigen dose to be administered non-invasively through the nose by means of highly adaptable carriers is chosen to be between 0.01x and 100x, more often between 0.05x and 75x, and even more preferably between 0.1x and 50x different from the corresponding immunogen/antigen dose that would have to be injected to achieve the desired biological effect.
43. The vaccine according to any one of claims 39 to 42 wherein the concentration of the transnasally administered adjuvant is between 10x lower and up to 1000x higher than that used with the corresponding subcutaneously injected formulations employing similar antigen, the transnasally administered immunoadjuvant concentration more often differing from the injected immunoadjuvant concentration by the factor between 0.5 and 100, or better, by the factor between 1 and 50, and best between 2 and 25.
44. A container comprising the pharmaceutical composition according to any one of claims 4 to 43.
45. A package comprising at least one container comprising the pharmaceutical composition of any one of claims 4 to 43.
46. A method for generating a protective immuno response on a mammal by vaccinating said mammal with a vaccine according to any one of claims 36 to 43.
47. The method according to claim 46 wherein different administration volumes are selected to control the applied immunogen dose and the outcome of vaccination.
48. The method according to claim 46 or 47, wherein a suspension of antigen-free penetrants is loaded with the antigen to be associated therewith during the day prior to an administration, preferably 360 min, more preferably 60 min and even more preferably 30 min before administering the resulting formulation in the nose.

49. The method of any one of claims 46 to 48 characterised in that at least one dose of vaccine is administered.
50. The method according to claim 49 wherein said vaccine is administered as a booster vaccination.
51. The method according to any one of claims 46 to 50, wherein the vaccine is applied between 2 and 10, preferably between 2 and 7, even more preferably up to 5 and most preferably up to 3 times, when a non-allergenic antigen is used, or such a number of times, in the case of allergens, as is required either to achieve the desired immuno-tolerance, determined according to a suitable assessment method, or else to deem the effort as having failed.
52. The method according to any one of claims 48 to 51, wherein the time interval between the subsequent vaccinations is chosen to be between 2 weeks and 5 years, often between 1 month and up to 3 years, more frequently between 2 months and 1.5 years.
53. The method according to any one of claims 46 to 52, wherein the flux of penetrants that carry an immunogen through the various pores in a well-defined barrier is determined as a function of a suitable driving force or a pressure acting across the barrier and the data are then conveniently described by a characteristic curve which, in turn, is employed to optimise the formulation or application further.